Testosterone Replacement Therapy (TRT) in Adult Men
Criteria for Use
February 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information.

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive TRT.*

- ☐ Severe untreated Obstructive Sleep Apnea (OSA) *see Issues*
- ☐ PSA >3.0 ng/mL or palpable prostate nodule or induration (including high risk populations: African-American, first-degree relative with prostate cancer or Agent Orange Exposure) if found to have active prostate cancer.
- ☐ Active prostate cancer
- ☐ Severe lower urinary tract symptoms (American Urological Association International Prostate Symptom Score [IPSS] >19) *see Issues*
- ☐ Uncontrolled or poorly controlled congestive heart failure
- ☐ Breast Cancer
- ☐ Men desiring fertility (unless prescribed for fertility by Urology)
- ☐ Hematocrit >50% at baseline; >54% at renewal
- ☐ History of venous thromboembolism
- ☐ History of hypersensitivity reactions to injectable or topical testosterone products
- ☐ History of anabolic steroid abuse or dependence
- ☐ Severe liver disease or severe renal disease *see Issues*
- ☐ **Transgender FtM patients only:** Pregnancy/suspected pregnancy (FDA Pregnancy Category X) or breast feeding

Inclusion Criteria [1,5]

- ☐ Prior to initiating TRT therapy, the potential risks and benefits should be discussed with the patient and the discussion documented in the medical record.
- ☐ Other potential treatable causes of symptoms have been addressed and suspected etiology has been documented.

AND One of the following:

- ☐ **Men with hypogonadism diagnosed by at least 1 specific clinical sign and symptom consistent with androgen deficiency AND unequivocal low serum testosterone levels.** *If patient is diagnosed outside of VHA without appropriate documentation of diagnosis, consider stopping testosterone therapy for 2-6 weeks (6 weeks if using injectable form) and retest for hypogonadism.*

  More specific Signs and Symptoms
  - Reduced or Low Libido
  - Decreased spontaneous erections
  - Loss of body (axillary, pubic, facial) hair
  - Smaller or shrinking testicles
  - Hot flashes/sweats
  - Inability to father children (testosterone will not treat infertility)
  - Low or zero sperm count
  - Low trauma fracture
  - Low bone mineral density
  - Gynecomastia, not otherwise explained

- ☐ Status post bilateral orchiectomy or unilateral orchiectomy (with documented atrophy or irradiation of second testicle) and cleared by Urology
- ☐ HIV-infected men with low testosterone levels and weight loss (see Issues)
- ☐ Men receiving high doses of glucocorticoids who have low testosterone levels (daily dose of at least 5-7.5 mg of prednisone or equivalent for at least 6 months)
- ☐ Klinefelter Syndrome, Kallmann Syndrome, or Pan-hypopituitarism and symptoms and signs of hypogonadism
- ☐ **Female-To-Male Transgender** (must meet safety criteria in addition to Transgender Cross Sex Hormone Therapy FtM)

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AND Baseline evaluation (except for transgender patients)

☐ Baseline labs within the past 12 months prior to initiation of TRT:

☐ Two baseline total serum testosterone levels, at least one week apart, between 8AM and 10AM of <300 ng/dL [not obtained during acute illness, and not on TRT for ≥2 weeks if on transdermal product or ≥ 6 weeks if on intramuscular product]. *Note: This is the lower threshold of normal testosterone levels measured by mass spectrometry. Use the lower end of normal testosterone levels as a threshold if other measurement methods are utilized.*

☐ If both serum testosterone levels near or below lower limit of normal, measure serum LH and FSH to determine if primary or secondary hypogonadism (may be measured concurrently with second testosterone level);

☐ Free or Bioavailable testosterone are acceptable alternatives; acceptable methods include equilibrium dialysis or calculated using the levels of SHBG and albumin.
Consider evaluation of free testosterone if patient is suspected of having altered Sex Hormone Binding Globulin (SHBG) concentrations, e.g. elderly or with obesity, diabetes, chronic illness, thyroid disease, etc.

☐ PSA, Hemoglobin and Hematocrit, Prolactin, LFT's, TSH

AND

☐ If male 45-75 years old with a baseline PSA ≥1.0 ng/mL perform Digital Rectal Exam (DRE) at baseline

Biologic females of childbearing potential who are transgender FtM: Pregnancy must be excluded in FtM transgender patients prior to receiving testosterone and patient provided contraceptive counseling on potential risk vs. benefit of taking testosterone if patient were to become pregnant.

Monitoring

- **Symptoms** Evaluate 3-6 months after initiation of TRT and then annually to assess if symptoms of hypogonadism have responded and to assess for adverse effects.
- **Testosterone level** Testosterone levels should be re-evaluated after 3-6 months of initiation of therapy and then annually in conjunction with symptom response. For injectable testosterone, measure level midway between injections. **Aim**: serum testosterone level in the mid-normal range for a eugonadal young male (approximately 500 ng/dL to 700 ng/dL). *Note: These are mid-range testosterone levels measured by mass spectrometry. Use the mid-range of normal testosterone levels if other measurement methods are utilized.*
- **Hematocrit** Re-evaluate HCT 3-6 months after initiating TRT and then annually. If >54% stop TRT until HCT decreases to a safe level and reinitiate therapy at a reduced dose.
- **CBC:** Natal females are especially at risk for increased erythropoiesis. Baseline and ongoing monitoring of CBC is recommended. See Transgender Cross-Sex Hormone Therapy Recommendations
- **PSA** For men 45-75 years old with a baseline PSA ≥ 1.0 ng/mL and normal DRE check PSA every 1-2 years in accordance with guidelines based on age and race.
  For men 45-75 years old with a baseline PSA < 1.0 ng/mL and normal DRE check PSA every 3-4 years in accordance with guidelines based on age and race.
  For men >75 years old with a baseline PSA < 3.0 ng/mL, normal DRE, and no other indications for biopsy, repeat PSA every 1-2 years.
- **LFT's:** After 3-6 months of therapy and then annually
- **Lipid profile:** At 6 months and then annually
- **Urologic Consultation** Recommended for an increase in PSA an absolute value of greater than 1.4 ng/mL within any 12 month period or a PSA velocity of more than 0.4 ng/mL-year using PSA at 6 months after initiation of TRT as reference, detection of abnormality on DRE, or an AUA/IPSS prostate symptom score of >19
- **Bone Mineral Density** Measure BMD of lumbar spine and/or femoral neck after 1-2 years of TRT in hypogonadal men with osteoporosis or low trauma fracture consistent with standard of care.

Issues for Consideration

- **Free testosterone levels** Consider evaluation of free testosterone when total testosterone is in the low normal range (200-400ng/dL) if patient is suspected of having altered Sex Hormone Binding Globulin (SHBG) concentrations, e.g. elderly or with obesity, diabetes, chronic illness, thyroid disease, etc.
- **Less Specific symptoms and signs:** the following signs and symptoms should trigger further evaluation. Use of these less specific signs and symptoms in conjunction with low serum testosterone levels to diagnose hypogonadism should be adjudicated locally:
  Depressed mood, Decreased energy, motivation, Self-confidence, Feeling sad or blue, Poor concentration and memory, Mild anemia (normochromic/normocytic in female range), Reduced muscle mass, Sleep disturbance Increase sleepiness, Reduced muscle bulk and strength, Increase body fat, body mass index, Diminished physical or work performance.
- **OSA** Use with caution in patients with treated OSA. TRT may increase pressure requirements in some patients although this may occur in a time dependent fashion and returns to baseline by 18 weeks of therapy.[2,3,4]
- **LUTS** Although patients with severe LUTS (IPSS score >19) is a relative contraindication to TRT, newer data suggests no difference in adverse events related to worsening LUTS between TRT and placebo in patients with mild to moderate range IPSS.[4]
- **HIV infected men** Short term TRT (generally 3-6 months) associated with gains in body weight, lean body mass, and muscle strength.
- **High dose glucocorticoids** Glucocorticoids for extended periods of time can decrease testosterone production.
- **Opioids** Concurrent opioid therapy can decrease testosterone levels.
- **Concomitant spironolactone** TRT should not be used routinely in patients on concomitant spironolactone therapy as spironolactone has anti-androgen effects; however, it is not a contraindication to therapy.

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- **Secondary Exposure**: There is a risk for secondary exposure when using topical testosterone gel products. This can be especially harmful to pregnant or breast-feeding women, and children. The application sites should be covered by a T shirt once the product is dry. Patients should wash their hands immediately after product application. Prior to direct skin-to-skin contact, patient should wash application area with soap and water to remove residue.
- **Venous thromboembolic events:** There have been post-marketing reports of venous thromboembolic events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), in patients using testosterone products. If a venous thromboembolic event is suspected, discontinue treatment and initiate appropriate workup and management.
- **Obesity**: Obesity can lower testosterone serum levels. Advise obese patients on weight loss techniques through diet and exercise.
- **Severe liver disease and severed renal disease**: While not a contraindication for testosterone therapy, either of these conditions puts patients at an increased risk for edema due to testosterone therapy.
- **FtM:** Testosterone therapy for transgender women may result in the continuation or initiation of menses. Testosterone is not an effective form of contraception and may not suppress menses. Refer to Transgender Cross Sex Hormone Therapy FtM for more guidance on both issues.
- **Cardiovascular Safety** The literature concerning the risk of adverse cardiovascular events with TRT has been conflicting; if there is a signal it is weak and requires more definitive studies. In 2014, the FDA issued a Drug Safety Communication that it was evaluating the risk of stroke, heart attack, and death with FDA-approved testosterone products based on the publication of 2 studies, one in VA patients.[5,6] Four meta-analyses, reviewing either all adverse events associated with TRT or cardiovascular events only in adult males of various ages reached different conclusions about the risk for cardiovascular events with TRT. [7,8,9,10] Three studies in VA patients also found conflicting results. In one study cited by the FDA, in a cohort of men in VA who underwent coronary angiography and had a serum testosterone level checked, those with low testosterone levels who subsequently received TRT had an increased risk of mortality, myocardial infarction or ischemic stroke compared to those with low serum testosterone levels who did not receive TRT.[4] The second study, an observational retrospective cohort study of men with low testosterone, compared total mortality in men who received TRT versus those who did not. Patients who received TRT had a decreased mortality compared to those with no treatment.[11] In the third retrospective cohort study which examined the effect of TRT on cardiovascular outcomes by comparing treated and untreated patients, TRT therapy in men with low testosterone levels and without a history of previous myocardial infarction or stroke might be associated with decreased risk of myocardial infarction, ischemic stroke, and all-cause mortality. Patients who received TRT but did not achieve a testosterone level in the therapeutic range did not see a reduction in the risk of myocardial infarction or stroke and had significantly less benefit in terms of mortality.[12] An ad-hoc analysis of older men in the Testosterone in Older Men with Mobility Limitations (TOM) trial found an increased risk of cardiovascular adverse events although this was not a planned outcome.[13] A large (n=55,593) cohort study from a commercial claims and encounters database of men who received TRT compared to men with prescriptions for PDE-5 inhibitors. There was an increased risk for myocardial infarction in the first 90 days after filling a TRT prescription and that risk declined to baseline in the 91-180 days after the initial TRT prescription although it is likely there was little use of TRT during the second time period. The increased risk was also seen in younger men receiving TRT with a history of heart disease but not in those without a history.[5] Another retrospective cohort study using a national sample of Medicare beneficiaries using injectable testosterone compared to a matched cohort not using testosterone found testosterone injection was not associated with a risk of MI. There was a protective effect of testosterone therapy in men at the highest risk for MI.[14] A randomized clinical trial of testosterone gel versus placebo evaluated subclinical atherosclerosis progression over 3 years of therapy in older men. Testosterone therapy did not result in a significant difference in the rates of change of subclinical atherosclerosis.[15] A recent thorough literature review addressed the key question of whether testosterone therapy is associated with increased cardiovascular risk. Although impossible to definitively evaluate the absolute safety of cardiovascular risk of testosterone therapy due to a lack of large, prospective, placebo-controlled trials of adequate duration, the review shows a strong relationship between higher serum testosterone levels (endogenous or exogenous) and beneficial reduction of cardiovascular disease and cardiovascular risk factors.[16] Finally, there is some data so suggest that the route of administration of TRT may alter the risk for cardiovascular adverse events, with a greater risk with injections compared to patches and gels.[17] The American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the association of testosterone therapy and cardiovascular risk concurred with the FDA that the retrospective cohort studies had major design flaws and limitations and the signal for cardiovascular risk is weak. They advise that large-scale prospective randomized controlled trials are needed that focus on cardiovascular benefits and risks of testosterone replacement therapy.[18]

Renewal Criteria

- If refill history and testosterone levels indicate adherence to therapy after initial 3-6 months (testosterone is a controlled substance and may be diverted)
- Documentation of improved hypogonadal symptoms
- For safety obtain Hgb/HCT, LFT's (3-6 months after initiation then annually), Lipid profile (annually) and perform DRE and PSA annually if > 40 years old and baseline PSA > 0.6 ng/mL
- PSA monitoring in accordance with baseline risk factors. Patients with PSA levels > 3.0 ng/mL should be further evaluated by Urology.
- If HCT is >54% stop therapy until HCT <50% then resume at lower dose or consider phlebotomy

Dose adjustment based on testosterone level: (after initial 3-6 months then annually)

- If level remains low but symptoms have improved, no dose change needed
- If no improvement in symptoms and testosterone is low (less than 400 ng/dL for topical or less than 500 ng/dL for injectable), consider dose titration
    - Topical Gel: increase by one pump per day; if at maximum of 4 pumps per day and no symptom improvement, consider change to injection
    - Testosterone injection: If testosterone is less than 500 ng/dL midway between injections and symptoms have not improved, increase dose OR decrease the dosing interval to every 10 days.
    - Testosterone patch: If no symptom improvement on 4mg/day patch, increase by adding 2mg/day patch
- If testosterone is more than 700 ng/dL on topical therapy or midway between injections, decrease the dose
- If levels are consistently > 1,000 ng/dL on lowest daily dose, therapy should be discontinued

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